Canadian Agency for Drugs and Technologies in Health

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CADTH OPTIMAL THERAPY REPORT

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Current Utilization of Second- and Third-Line Therapies in Patients with Type 2 Diabetes

Supporting Informed Decisions

External Consultants

CADTH staff would like to thank the following people for their time, assistance, and expert input throughout the project, including guidance on the approach and methods as well as constructive feedback on drafts of this report.

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Conflicts of Interest

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None of the other CERC members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.

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ABBREVIATIONS

CAC	COMPUS Advisory Committee
CADTH	Canadian Agency for Drugs and Technologies in Health
CERC	COMPUS Expert Review Committee
DPP-4	dipeptidyl peptidase-4
OPDP	Ontario Public Drug Program
PDP	private drug plan
TZD	thiazolidinedione

GLOSSARY

A1C: A glycosylated form of hemoglobin, formed by the attachment of sugars to the hemoglobin molecule when glucose levels are elevated. A1C levels increase with the average concentration of glucose in the blood.

Diabetes: A group of common metabolic disorders characterized by hyperglycemia and caused by insufficient insulin secretion, reduced insulin sensitivity of target tissues, or both.

Effectiveness: The extent to which an intervention, procedure, regimen, or service produces the intended outcomes when deployed under routine (real-world) circumstances.

Hyperglycemia: A qualitative term used to describe blood glucose that is above the normal range.

Hypoglycemia: A qualitative term used to describe blood glucose that is below the normal range. Definitions vary across studies, although one or more of the following is usually required to define a hypoglycemic event: autonomic or neuroglycopenic symptoms characteristic of low blood glucose (e.g., trembling, sweating, hunger, confusion, weakness) that respond to carbohydrate intake, and/or a plasma glucose level below a specific value (threshold is usually between 3.4 mmol/L and 4.0 mmol/L).

Incretin agents: Therapeutics that promote glycemic control through potentiation of the incretin system. Glucagon-like peptide-1 analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors are examples of incretin agents.

Long-acting insulin analogues: A class of insulin analogues that is produced by introducing alterations in the amino acid sequence of human insulin. They do not mimic basal endogenous insulin secretion; rather, they promote a prolonged, non-fluctuating basal level of insulin activity.

Rapid-acting insulin analogues: A class of insulin analogues that is produced by introducing alterations in the amino acid sequence of human insulin, which more closely mimics the short duration of action of meal-induced endogenous insulin in non-diabetic patients than does regular human insulin.

Systematic review: A summary of the medical literature that uses explicit methods to identify, select, appraise, and analyze studies relevant to a particular clinical question.

Thiazolidinedione: A class of drugs sometimes referred to as “glitazones,” used to treat type 2 diabetes by decreasing insulin resistance. Chemically, the members of this class are derivatives of the parent compound thiazolidinedione, and include rosiglitazone and pioglitazone.

Type 2 diabetes: Diabetes characterized by insulin resistance and varying degrees of insulin deficiency, especially as the diabetes progresses.

1 INTRODUCTION

In March 2004, the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) was launched by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) — now the Canadian Agency for Drugs and Technologies in Health (CADTH) — as a service to federal, provincial, and territorial jurisdictions and other stakeholders. COMPUS is a nationally coordinated program funded by Health Canada.

The goal of CADTH, through COMPUS is to optimize drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use. Where possible, CADTH builds on existing applicable Canadian and international initiatives and research. CADTH goals are achieved through three main approaches:

- identifying evidence-based optimal therapy in prescribing and use of specific drugs
- identifying gaps in clinical practice
- proposing evidence-based interventions to address the gaps and supporting the implementation of the interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- The COMPUS Advisory Committee (CAC), which includes representatives from the federal, provincial, and territorial health ministries and related health organizations.
- The COMPUS Expert Review Committee (CERC), members are listed at the beginning of this document.
- Stakeholder feedback.

1.1 COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office and three or more Specialist Experts appointed to provide their expertise in recommending optimal therapy for one or more specific topics (at the beginning of this document). For the insulin analogues and blood glucose test strips, four endocrinologists or diabetes specialists were appointed as Specialist Experts. Two of the Core Members are Public Members who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization expertise, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members, including Public Members, are appointed by the CADTH Board of Directors.

The mandate of CERC is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. CERC develops recommendations and advice with the aim of contributing to optimal health outcomes and fostering a sustainable health care system for Canadians. CERC considers the practical needs of policy-makers, health care providers, and consumers in implementing and using the recommendations and advice toward the promotion of optimal practices. The overall perspective used by CERC members in producing recommendations is that of public

health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 THE ISSUE

CAC has identified the management of diabetes as being a priority area for optimal practice initiatives based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- benefit to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use.

Within diabetes management, second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy was identified by CAC as a priority topic.

The treatment of patients with type 2 diabetes usually begins with lifestyle modifications and treatment with oral antidiabetes drugs. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone.[1-5] Recent utilization data indicate that approximately 60% of patients with type 2 diabetes initiating pharmacotherapy in Canada are started on metformin monotherapy.[6] As type 2 diabetes is a progressive disease, glycemic levels are likely to worsen over time. Most patients eventually require two or more oral antidiabetes drugs, or the addition of an insulin regimen, to achieve or maintain target blood glucose levels.[7,8] Existing guidelines and consensus documents[1-3,9-15] vary with respect to recommendations for second-line treatment after glycemic control cannot be achieved with metformin alone. Some recommend that a sulfonylurea be added to metformin.[3,11,12,15] Others, however, do not identify a single drug class or agent as being preferred; instead, a stepwise approach to add agents from various classes is often recommended.[1,2,9,10,13,14] Little or no evidence is cited in relation to recommendations regarding second-line therapy in any of the guidelines.

Canadians spent approximately $17.10 per capita on oral antidiabetes drugs in 2007, for a total of $563 million.[16] The average cost per oral antidiabetes drug prescription in publicly funded drug plans in Canada nearly doubled over the course of a decade, from $11.31 in 1998 to $20.77 in 2007.[6] The increase in costs may have at least partly been due to the introduction of more costly antidiabetes drugs to the market. For example, the thiazolidinediones (TZDs) (i.e., rosiglitazone and pioglitazone) represented only 9.4% of all prescriptions for antidiabetes drugs in 2008, yet they accounted for 33% of total expenditures.[17] Given the large, growing population of patients with type 2 diabetes in Canada, suboptimal use of second-line antidiabetes drugs is likely to have a detrimental effect on both health outcomes and the cost-effective use of drugs. Therefore, there is a need for clear recommendations based on clinical and cost-effectiveness evidence to guide second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy.

2.1 Diabetes

Diabetes is a chronic disease characterized by the body's inability to produce sufficient insulin and/or properly use insulin.[18] Type 1 diabetes occurs in approximately 10% of patients with diabetes, and it results when little or no insulin is produced by the body.[19] Type 2 diabetes is a metabolic disorder caused by varying degrees of insulin resistance; the body usually produces insulin but is unable to use it properly.[19] When inadequately managed, diabetes is likely to result in poor glycemic control.[18] Impaired glycemic control, if prolonged, may result in diabetes-related complications (e.g., ischemic heart disease, stroke, blindness, end-stage renal disease, and lower limb amputation).[20,21]

It is estimated that 1.9 million Canadian men and women had been diagnosed with diabetes in 2005 to 2006, representing 6.2% of all men and 5.5% of all women. In addition, it is believed that a large number of Canadians have diabetes but have not been diagnosed.[22]

2.1.1 Management of blood glucose levels in type 2 diabetes

One goal of diabetes management is to maintain control of blood glucose levels to reduce the patient's risk of developing long-term diabetes-related complications. Lifestyle modifications (i.e., weight control, proper nutrition, and adequate exercise) and use of antidiabetes drugs such as oral agents or insulin are recommended approaches for improving glycemic control.[1]

a) Technology description — Second-line antidiabetes drugs

Eleven classes of antidiabetes drugs are available as second-line therapy for patients with type 2 diabetes inadequately controlled on metformin monotherapy: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, TZDs, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 analogues, basal insulins, bolus insulins, biphasic insulins, weight loss agents, and amylin analogues (Table 1). Glucagon-like peptide-1 analogues and amylin analogues are currently not available in Canada. Agents from all classes were included in the systematic review as long as they were approved for use by Health Canada, the United States Food and Drug Administration, or the European Medicines Agency.

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Administration**	**Relevant Indications**
Sulfonylureas			
Gliclazide / Gliclazide MR	Range: 80 mg to 320 mg DDD: 160 mg Range for MR: 30 mg to 120 mg	Oral	Control of hyperglycemia in gliclazide-responsive type 2 diabetes, which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.[23,24]
Glimepiride	Range: 1 mg to 8 mg DDD: 2 mg	Oral	Indicated for use as follows: as an adjunct to proper dietary management, exercise, and weight reduction to lower the blood glucose in patients with type 2 diabetes who have hyperglycemia that cannot be controlled by diet and exercise alone; in combination with metformin when diet and exercise and glimepiride or metformin alone do not result in adequate glycemic control; in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent alone.[25]
Glyburide	Range: 2.5 mg to 20 mg DDD: 10 mg	Oral	Indicated as an adjunct to proper dietary management, exercise, and weight reduction to lower blood glucose in adult patients with type 2 diabetes who have hyperglycemia that cannot be controlled by diet and exercise alone or when insulin therapy is not required.[26]
Chlorpropamide	Range: 100 mg to 500 mg DDD: 375 mg	Oral	In mild, stable type 2 diabetes to control hyperglycemia responsive to the drug. It should not be used in those patients who are prone to ketosis or who can be controlled by dietary management and exercise alone or for whom insulin therapy is more appropriate.[27]
Glipizide	Range: 5 mg to 40 mg DDD: 10 mg	Oral	Not approved in Canada
Tolbutamide	Range: 500 mg to 3,000 mg DDD: 1,500 mg	Oral	To control hyperglycemia in tolbutamide-responsive type 2 diabetes, which cannot be controlled by proper dietary management and exercise or when insulin therapy is not appropriate.[28]
Thiazolidinediones			
Pioglitazone	Range: 15 mg to 45 mg DDD: 30 mg	Oral	Indicated as monotherapy in patients not controlled by diet and exercise alone, to decrease insulin resistance and blood glucose levels in patients with type 2 diabetes. Also indicated for use in combination with a sulfonylurea or metformin when diet and exercise plus the single agent do not result in adequate glycemic control.[29]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Administration**	**Relevant Indications**
Rosiglitazone	Range: 4 mg to 8 mg DDD: 6 mg	Oral	Indicated for use as an adjunct to diet and exercise in patients with type 2 diabetes as follows: monotherapy in patients not controlled by diet and exercise alone and for whom metformin is inappropriate because of contraindications or intolerance; in combination with metformin when diet and exercise plus metformin do not result in adequate glycemic control; in combination with a sulfonylurea in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus sulfonylurea or rosiglitazone monotherapy do not result in adequate glycemic control.[30]
Meglitinides			
Nateglinide	Range: 60 mg to 120 mg DDD: 360 mg	Oral	Indicated as monotherapy to lower the blood sugar in patients with type 2 diabetes not controlled satisfactorily by diet and exercise alone. Also indicated in combination with metformin in patients whose diabetes is not controlled satisfactorily with diet, exercise, or metformin alone.[31]
Repaglinide	Range: 0.5 mg to 16 mg DDD: 4 mg	Oral	Indicated in patients with type 2 diabetes who have hyperglycemia that cannot be controlled satisfactorily by diet and exercise alone. Indicated in combination therapy with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus metformin monotherapy. Indicated in combination with rosiglitazone in patients who show intolerance to metformin or for whom metformin is contraindicated, when diet and exercise plus rosiglitazone or repaglinide monotherapy do not result in adequate glycemic control.[32]
Alpha-glucosidase inhibitors			
Acarbose	Range: 150 mg to 300 mg DDD: 300 mg	Oral	Indicated for use as follows: as an adjunct to prescribed diet for the management of blood glucose levels in patients with type 2 diabetes inadequately controlled by diet alone; in combination with either a sulfonylurea, metformin or insulin to improve glycemic control in patients with type 2 diabetes inadequately controlled on diet, exercise and either a sulfonylurea, metformin or insulin alone.[33]
Miglitol	Range: 75 mg to 300 mg DDD: 300 mg	Oral	Not approved in Canada
DPP-4 inhibitors			
Sitagliptin	Dosage: 100 mg DDD: 100 mg	Oral	Indicated in combination with metformin in adult patients with type 2 diabetes inadequately controlled with metformin monotherapy.[34]

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Administration**	**Relevant Indications**
Vildagliptin	Dosage: 100 mg DDD: 100 mg	Oral	Not approved in Canada
Saxagliptin	Dosage: 5 mg DDD: NA	Oral	Indicated in patients with type 2 diabetes to improve glycemic control in combination with metformin or a sulfonylurea, when metformin or the sulfonylurea used alone, with diet and exercise, does not provide adequate glycemic control.[35]
GLP-1 analogues			
Exenatide	Range: 10 µg to 20 µg DDD: 15 µg	SC	Not approved in Canada
Liraglutide	Range: 1.2 mg to 1.8 mg DDD: NA	SC	Not approved in Canada
Rapid-acting insulin analogues			
Insulin aspart	Dosage is individualized	SC	Patients with diabetes who require insulin for the maintenance of normal glucose homeostasis. Insulin aspart should normally be used in regimens together with an intermediate or long-acting insulin.[36]
Insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with diabetes who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes.[37]
Insulin glulisine	Dosage is individualized	SC	Indicated for the treatment of adult patients with type 2 diabetes where treatment with insulin is required.[38]
Short-acting human insulin			
Regular human insulin	Dosage is individualized	SC	For the treatment of insulin-requiring patients with diabetes.
Intermediate-acting insulin			
Insulin NPH	Dosage is individualized	SC	For the treatment of insulin-requiring patients with diabetes.
Long-acting insulin analogues			
Insulin detemir	Dosage is individualized	SC	Indicated for the treatment of adult patients with type 2 diabetes who require a basal insulin for the control of hyperglycemia and indicated for the treatment of type 2 diabetes in combination with oral antidiabetes drugs (metformin, sulfonylureas, or a TZD) in adult patients who are not in adequate metabolic control on oral antidiabetes drugs alone.[39]
Insulin glargine	Dosage is individualized	SC	Indicated for once-daily subcutaneous administration in the treatment of patients (> 17 years of age) with type 2 diabetes who require basal insulin for the control of hyperglycemia.[40]
Insulin NPL	Dosage is individualized	SC	Not approved in Canada

Table 1: Drugs Included in the Therapeutic Review			
Generic Name	**Dosage**	**Method of Administration**	**Relevant Indications**
Premixed insulins			
Premixed regular NPH	Dosage is individualized	SC	For the treatment of insulin-requiring patients with diabetes.
Biphasic insulin aspart	Dosage is individualized	SC	Indicated for the treatment of adult patients with diabetes who require insulin for the maintenance of normal glucose homeostasis.[41]
Biphasic insulin lispro	Dosage is individualized	SC	Indicated for the treatment of patients with diabetes who require insulin for the maintenance of normal glucose homeostasis. Also indicated for the initial stabilization of diabetes.[37]
Weight loss agents			
Orlistat	Dosage: 360 mg DDD: 360 mg	Oral	Orlistat, when used in conjunction with a mildly hypocaloric diet, is indicated for obesity management, including weight loss and weight maintenance and reducing the risk of weight regain in obese patients after prior weight loss. These indications apply to obese patients with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia, excess visceral fat). Orlistat can be used in combination with antidiabetes drugs (sulfonylureas, metformin, insulin) to improve blood glucose control in overweight or obese type 2 diabetes patients inadequately controlled on diet, exercise, and one or more of a sulfonylurea, metformin, or insulin.[42]
Sibutramine	Range: 10 mg to 15 mg DDD: 10 mg	Oral	Indicated as adjunctive therapy within a weight management program for obese patients with an initial BMI of 30 kg/m^2 or higher and obese patients with an initial BMI of 27 kg/m^2 or higher in the presence of other risk factors (e.g., controlled hypertension, type 2 diabetes, dyslipidemia, visceral fat).[43]
Amylin Analogues			
Pramlintide	Range: 60 µg to 120 µg	SC	Not approved in Canada

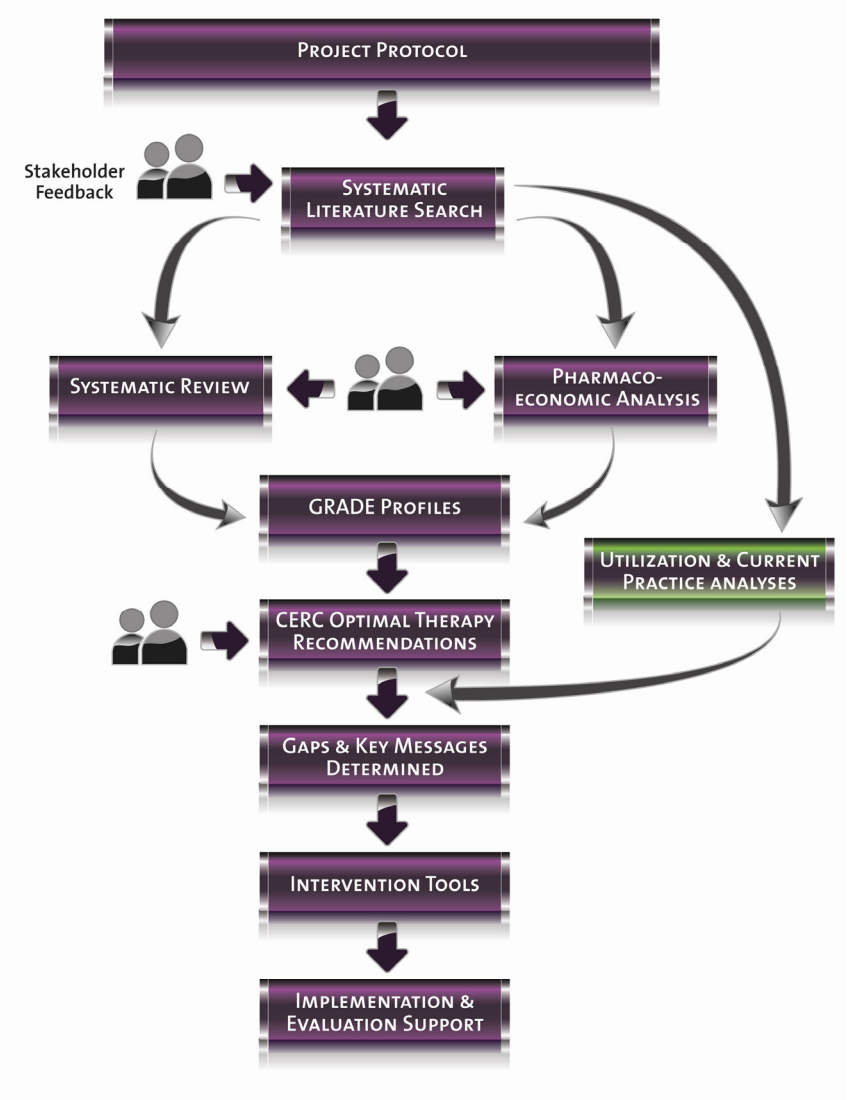
BMI = body mass index; DDD = defined daily dose (as per the World Health Organization); DPP-4 = dipeptidyl peptidase-4; GLP = glucagon-like peptide-1; MR = modified release; NA = not applicable; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; SC = subcutaneous; TZD = thiazolidinedione.

3 OBJECTIVE

To examine how the oral antihyperglycemic market has changed in Canada since the introduction of newer more expensive oral agents. Also, to identify current utilization patterns of second-line and third-line therapies in patients with type 2 diabetes inadequately controlled on metformin monotherapy or combination therapy with metformin and sulfonylureas in Canada.

4 PROJECT OVERVIEW

Once a topic is selected, staff undertakes activities related to key areas in the CADTH procedure. The CAC provides advice and guidance throughout the process, from topic identification through to supporting intervention and evaluation tools. CERC, as described in Section 1.1, provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of medications. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.



To identify and promote the implementation of evidence-based and cost-effective therapy in the prescribing and use of second-line antidiabetes drugs for patients with type 2 diabetes inadequately controlled on metformin monotherapy, CADTH follows the process outlined in the flow chart to the right.

This report represents the Current Utilization (green box).

Market Share Analysis

5 METHODS

5.1 Study Design and Data Sources

We conducted a retrospective cross-sectional time-series analysis of oral antidiabetes drugs reimbursed by the Ontario Public Drug Plan (OPDP) and private drug plans (PDPs) in Canada during a 12-year period (1998 to 2009). Aggregate-level data were provided by Brogan Inc.[44] The Brogan Inc. database is the largest drug claims database in Canada and is comprised of aggregate and claims level data collected from public drug plans in Canada and more than 17 major PDPs.

5.2 Statistical Analysis

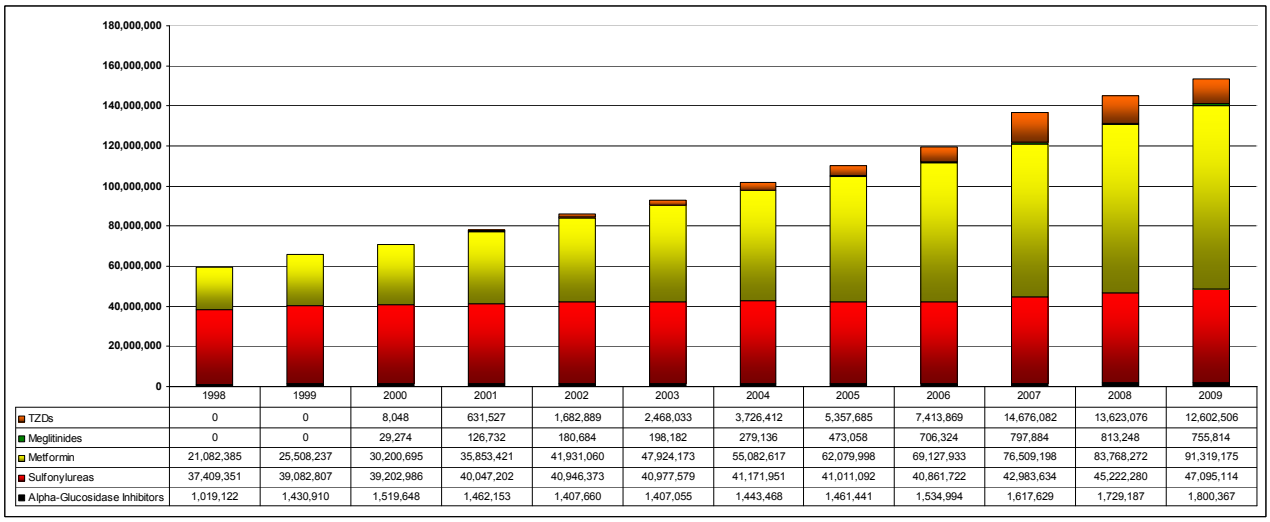
For each year between 1998 and 2009, we determined days supply and total expenditure for each class of oral antidiabetes drugs in Canada: metformin, sulfonylureas, TZDs, alpha-glucosidase inhibitors, meglitinides, and DPP-4 inhibitors. For 2009, we calculated days supply, total expenditure, average cost per unit, average cost per year, and the number of patients that could be treated with the lowest cost alternative for each class of oral antidiabetes drugs. All analyses were stratified by PDPs and the OPDP. We also determined the percentage change in terms of day supply and expenditure for each oral antidiabetes drug class between 2007 and 2008 as well as 2008 and 2009.

6 RESULTS (MARKET SHARE)

6.1 Ontario Public Drug Program

Days supply of oral antidiabetes drugs in the OPDP increased from 59.5 million in 1998 to 153.6 million in 2009. Large increases in oral antidiabetes drug use were driven primarily by increases in use of metformin, as days supply of metformin increased from 21.1 million in 1998 to 91.3 million in 2009. Increases in total oral antidiabetes drug use were also driven by increases in use of TZDs. The use of TZD increased from 14.7 million in 2007 following their introduction in 2000. Use of TZDs, however, decreased from 14.7 million in 2007 to 12.6 million in 2009, likely due to drug safety warnings surrounding the use of rosiglitazone. From 2007 to 2009, use of sulfonylureas and alpha-glucosidase increased from 43.0 million to 47.1 million and 1.6 million to 1.8 million respectively (Figure 2).

Figure 2: Use of Oral Antidiabetes Drugs (days supply) in the OPDP from 1998 to 2009

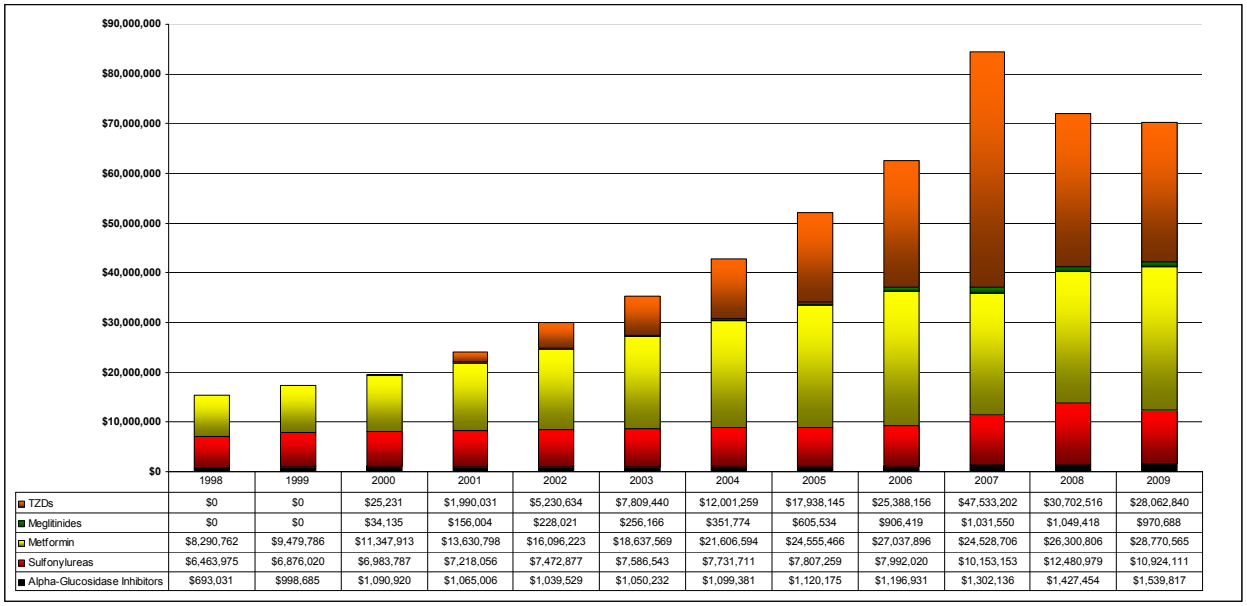


	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
TZDs	0	0	8,048	631,527	1,682,889	2,468,033	3,726,412	5,357,685	7,413,869	14,676,082	13,623,076	12,602,506
Meglitinides	0	0	29,274	126,732	180,684	198,182	279,136	473,058	706,324	797,884	813,248	755,814
Metformin	21,082,385	25,508,237	30,200,695	35,853,421	41,931,060	47,924,173	55,082,617	62,079,998	69,127,933	76,509,198	83,768,272	91,319,175
Sulfonylureas	37,409,351	39,082,807	39,202,986	40,047,202	40,946,373	40,977,579	41,171,951	41,011,092	40,861,722	42,983,634	45,222,280	47,095,114
Alpha-Glucosidase Inhibitors	1,019,122	1,430,910	1,519,648	1,462,153	1,407,660	1,407,055	1,443,468	1,461,441	1,534,994	1,617,629	1,729,187	1,800,367

OPDP = Ontario Public Drug Plan; TZDs = thiazolidinediones.

Total expenditure on oral antidiabetes drugs in the OPDP increased from $15.4 million in 1998 to $84.5 million in 2007, and then dropped to $70.2 million in 2009. Large increases in the total oral antidiabetes drug expenditure were driven primarily by increases in expenditures on TZDs. Following their introduction in 2000, expenditures on TZDs increased to $47.5 million in 2007. Expenditure on TZDs, however, decreased from $47.5 million in 2007 to $28.0 million in 2009; this was likely due to drug safety warnings surrounding the use of rosiglitazone and the introduction of generic pioglitazone (Figure 3).

Figure 3: Expenditure on Oral Antidiabetes Drugs in OPDP from 1998 to 2009



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
TZDs	$0	$0	$25,231	$1,990,031	$5,230,634	$7,809,440	$12,001,259	$17,938,145	$25,388,156	$47,533,202	$30,702,516	$28,062,840
Meglitinides	$0	$0	$34,135	$156,004	$228,021	$256,166	$351,774	$605,534	$906,419	$1,031,550	$1,049,418	$970,688
Metformin	$8,290,762	$9,479,786	$11,347,913	$13,630,798	$16,096,223	$18,637,569	$21,606,594	$24,555,466	$27,037,896	$24,528,706	$26,300,806	$28,770,565
Sulfonylureas	$6,463,975	$6,876,020	$6,983,787	$7,218,056	$7,472,877	$7,586,543	$7,731,711	$7,807,259	$7,992,020	$10,153,153	$12,480,979	$10,924,111
Alpha-Glucosidase Inhibitors	$693,031	$998,685	$1,090,920	$1,065,006	$1,039,529	$1,050,232	$1,099,381	$1,120,175	$1,196,931	$1,302,136	$1,427,454	$1,539,817

OPDP = Ontario Public Drug Plan; TZDs = thiazolidinediones.

Metformin and sulfonylureas were the most widely used oral antidiabetes drugs in the OPDP in 2009, accounting for 56.0% and 31.5% of total days supply respectively. Metformin and sulfonylureas, however, accounted for 40.9% and 15.5% of the total expenditure on oral antidiabetes drugs respectively. A large proportion of total costs were expended on TZDs (39.9%). TZDs are the most expensive oral antidiabetes drug currently reimbursed in the OPDP; the mean annual cost of patients using TZDs in 2009 was $698. In contrast, the mean annual cost of patients using metformin or a sulfonylurea in 2009 was $137 and $93 respectively. Therefore, you could treat[1] eight patients with a sulfonylurea for every patient you treat with a TZD (Table 2).

Table 2: Treatment with Lowest Cost Alternative on Each Oral Antidiabetes Drug Class in the OPDP (2009)

Drug Class	Days Supply	Expenditure (C$) (%)	Mean Cost per Patient-Year* ($)	Number of Patients Who Could Be Treated with Low Cost Alternative†
Alpha-Glucosidase Inhibitors	1,617,629 (1.2%)	1,539,817 (2.2%)	347	4
Sulfonylureas	42,983,634 (31.5%)	10,924,111 (15.5%)	93	1
Metformin	76,509,198 (56.0%)	28,770,565 (40.9%)	137	1
Meglitinides	797,884 (0.6%)	970,688 (1.4%)	444	5
TZDs	14,676,082 (10.7%)	28,062,840 (39.9%)	698	8

OPDP = Ontario Public Drug Plan; TZDs = thiazolidinediones.
*Does not include the additional cost of blood glucose test strips.
†Calculated relative to average annual expenditure on sulfonylureas.

From 2007 to 2008, the days supply (−7.2%) and expenditure (−35.4%) on TZDs decreased in the OPDP. Days supply and expenditure on other oral diabetes drugs increased from 2007 to 2008 (Table 3). From 2008 to 2009, the days supply (−7.5%) and expenditure (−8.6%) on TZDs decreased while the days supply of sulfonylureas, metformin, and alpha-glucosidase inhibitors increased by 4.1%, 9% and 4.1% respectively. Expenditures on metformin and alpha-glucosidase inhibitors increased; however, expenditure on sulfonylureas decreased by 12.5% despite an increase in use, likely attributable to gliclazide modified release becoming available as a generic in 2008 (Table 3).

[1] Does not include the additional cost of blood glucose test strips.

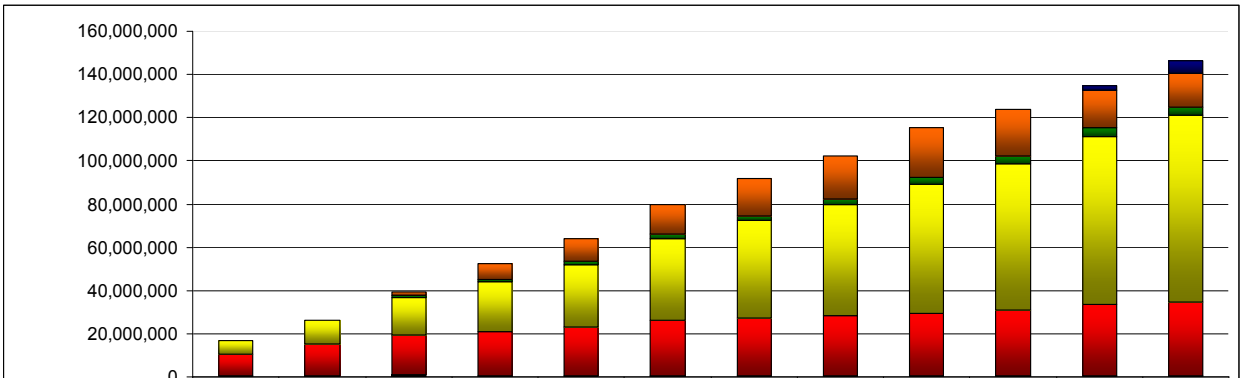
Table 3: Percentage Increase in Days Supply and Total Expenditure on Oral Antidiabetes Drugs by Drug Class between 2007-2008 and 2008-2009 in the OPDP				
Drug Class	**2007 to 2008**		**2008 to 2009**	
	Increase, Days Supply	**Increase, Expenditure**	**Increase, Days Supply**	**Increase, Expenditure**
Alpha-Glucosidase Inhibitors	6.9%	9.6%	4.1%	7.9%
Sulfonylureas	5.2%	22.9%	4.1%	−12.5%*
Metformin	9.5%	7.2%	9.0%	9.4%
Meglitinides	1.9%	1.7%	−7.1%	−7.5%
TZDs	−7.2%	−35.4%	−7.5%	−8.6%

OPDP = Ontario Public Drug Plan; TZDs = thiazolidinediones.
*Decrease in expenditure, despite increase in days supply, likely attributable to gliclazide modified release becoming available as a generic drug in 2008.

6.2 Private Drug Plans in Canada

Days supply of oral antidiabetes drugs in PDPs increased from 17.0 million in 1998 to 146.1 million in 2009. Large increases in oral antidiabetes drug use were driven primarily by increases in use of metformin, as days supply of metformin increased from 6.7 million in 1997 to 86.2 million in 2009. Increases in total oral antidiabetes drug use were also driven by increases in use of TZDs. The use of TZD increased to 21.3 million in 2007. Use of TZDs, however, decreased from 21.3 million in 2007 to 15.7 million in 2009, likely due to drug safety warnings surrounding the use of rosiglitazone. From 2007 to 2009, the use of sulfonylureas, alpha-glucosidase, and DPP-4 inhibitors increased (Figure 4).

Figure 4: Use of Oral Antidiabetes Drugs (days supply) in PDPs from 1998 to 2009



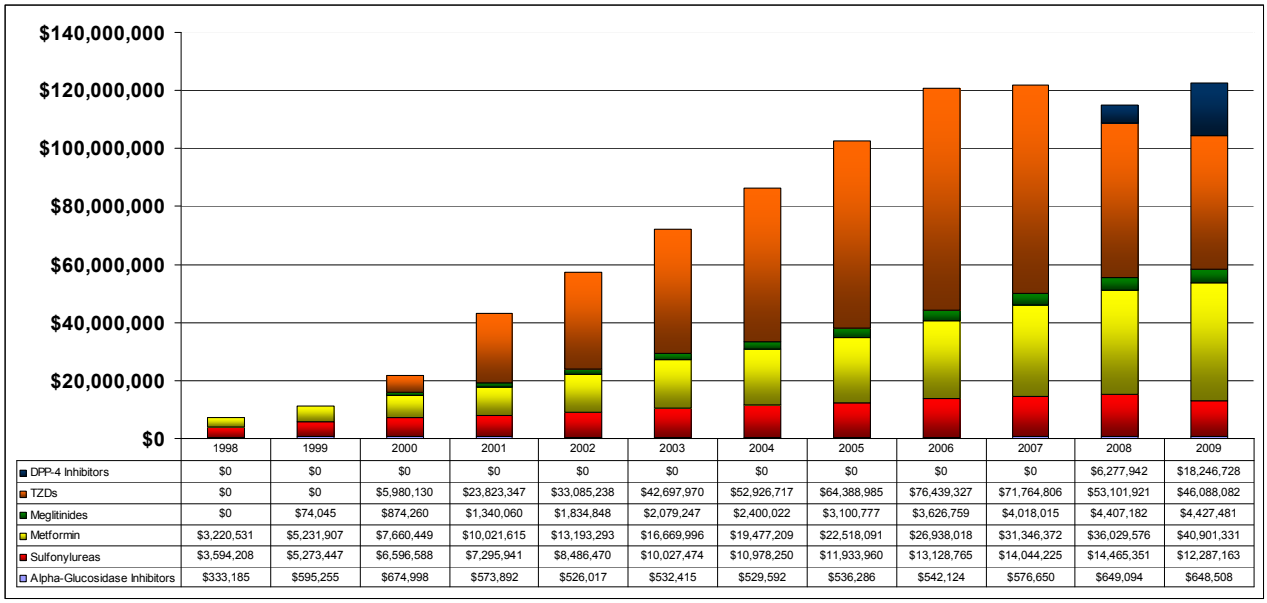
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
DPP-4 Inhibitors	0	0	0	0	0	0	0	0	0	0	1,969,584	5,694,813
TZDs	0	0	1,763,372	7,488,239	10,538,661	13,961,272	17,190,294	20,169,300	23,303,198	21,260,775	17,522,961	15,713,104
Meglitinides	0	77,826	822,372	1,266,408	1,634,539	1,886,231	2,214,399	2,779,868	3,180,290	3,471,075	3,739,062	3,669,005
Metformin	6,726,012	11,237,167	17,251,216	22,708,467	28,759,991	37,688,503	44,639,093	51,265,294	59,460,458	67,782,677	78,089,913	86,218,992
Sulfonylureas	9,806,008	14,366,147	18,551,645	20,497,937	22,464,954	25,734,650	26,834,326	27,626,226	28,953,418	30,397,029	32,608,909	34,126,053
Alpha-Glucosidase Inhibitors	446,083	783,901	884,722	743,420	672,216	684,242	666,856	656,590	648,989	692,150	753,017	726,214

DPP-4 = dipeptidyl peptidase-4; PDPs = private drug plan; TZDs = thiazolidinediones.

Total expenditures on oral antidiabetes drugs in PDPs increased from $7.1 million in 1998 to $122.6 million in 2009. Large increases in oral antidiabetes drug use were driven primarily by

increases in the use of metformin, as the expenditure on TZDs increased to $74.6 million in 2006. Expenditure on TZDs, however, decreased from $76.4 million in 2006 to $46.1 million in 2009; that is likely due to drug safety warnings surrounding the use of rosiglitazone and the introduction of generic pioglitazone and DPP-4s (Figure 5). However, the expenditure on DPP-4 inhibitors increased to $18.2 million following their introduction in 2008 (Figure 5).

Figure 5: Expenditure on Oral Antidiabetes Drugs in PDP from 1998 to 2009



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
DPP-4 Inhibitors	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$6,277,942	$18,246,728
TZDs	$0	$0	$5,980,130	$23,823,347	$33,085,238	$42,697,970	$52,926,717	$64,388,985	$76,439,327	$71,764,806	$53,101,921	$46,088,082
Meglitinides	$0	$74,045	$874,260	$1,340,060	$1,834,848	$2,079,247	$2,400,022	$3,100,777	$3,626,759	$4,018,015	$4,407,182	$4,427,481
Metformin	$3,220,531	$5,231,907	$7,660,449	$10,021,615	$13,193,293	$16,669,996	$19,477,209	$22,518,091	$26,938,018	$31,346,372	$36,029,576	$40,901,331
Sulfonylureas	$3,594,208	$5,273,447	$6,596,588	$7,295,941	$8,486,470	$10,027,474	$10,978,250	$11,933,960	$13,128,765	$14,044,225	$14,465,351	$12,287,163
Alpha-Glucosidase Inhibitors	$333,185	$595,255	$674,998	$573,892	$526,017	$532,415	$529,592	$536,286	$542,124	$576,650	$649,094	$648,508

DPP-4 = dipeptidyl peptidase-4; PDP = private drug plan; TZDs = thiazolidinediones.

Metformin and sulfonylureas were the most widely used oral drugs in PDPs in 2009, accounting for 59% and 23.4% of total days supply. Metformin and sulfonylureas, however, accounted for 33.4% and 10% of the total expenditure respectively. A large proportion of total costs were expended on TZDs (37.6%) and DDP-4 inhibitors (14.9%). TZDs and DDP-4 inhibitors are the most expensive oral antidiabetes drugs; the average annual cost of patients using TZDs or DPP-4 inhibitors in 2009 was $1,071 and $1,169 respectively. In contrast, the average annual cost of patients using metformin or a sulfonylurea in 2009 was $131 and $173 respectively. Therefore, you could treat[2] eight or nine patients with a sulfonylurea or metformin for every patient you treat with either a TZD or a DPP-4 inhibitor respectively (Table 4).

[2] Does not include the additional cost of blood glucose test strips.

Table 4: Utilization and Expenditure on Each Oral Antidiabetes Drug Class in OPDP (2009)				
Drug Class	**Days Supply**	**Expenditure (C$) (%)**	**Mean Cost per Patient-Year* ($)**	**Number of Patients Who Could be Treated with Low Cost Alternative†**
Alpha-Glucosidase Inhibitors	726,214 (0.5%)	648,508 (0.5%)	326	2
Sulfonylureas	34,126,053 (23.4%)	12,287,163 (10.0%)	131	1
Metformin	86,218,992 (59.0%)	40,901,331 (33.4%)	173	1
Meglitinides	3,669,005 (2.5%)	4,427,481 (3.6%)	440	3
TZDs	15,713,104 (10.8%)	46,088,082 (37.6%)	1,071	8
DPP-4 inhibitors	5,694,813 (3.9%)	18,246,728 (14.9%)	1,169	9

DPP-4 = dipeptidyl peptidase-4; OPDP = Ontario Public Drug Plan; TZDs = thiazolidinediones.
*Does not include the additional cost of blood glucose test strips.
†Calculated relative to average annual expenditure on sulfonylureas.

From 2007 to 2008, there was a decrease in days supply (−17.8%) and expenditure (−26%) on TZDs in PDPs. Days supply and expenditure on other oral diabetes drugs increased from 2007 to 2008 (Table 5). From 2008 to 2009, days supply (−10.3%) and expenditure (−13.2%) on TZDs decreased, albeit at a lower rate than from 2007 to 2008; days supply of sulfonylureas, metformin, and DPP-4 inhibitors increased by 4.7%, 10.4% and 189% respectively. Expenditures on metformin and DPP-4 inhibitors decreased; however, expenditure on sulfonylureas decreased by 15.1% despite an increase in use, likely attributable to gliclazide modified release becoming available as a generic in 2008 (Table 5).

Table 5: Percentage Increase in Days Supply and Total Expenditure on Oral Antidiabetes Drugs by Drug Class Between 2007-2008 and 2008-2009				
Drug Class	**2007 to 2008**		**2008 to 2009**	
	Increase, Days Supply (%)	**Increase, Expenditure (%)**	**Increase, Days Supply (%)**	**Increase, Expenditure (%)**
Alpha-Glucosidase Inhibitors	8.8%	12.6%	−3.6%	−0.1%
Sulfonylureas	7.3%	3.0%	4.7%	−15.1%*
Metformin	15.2%	14.9%	10.4%	13.5%
Meglitinides	7.7%	9.7%	−1.9%	0.5%
Glitazones	−17.6%	−26.0%	−10.3%	−13.2%
DPP-4-inhibitors	NA	NA	189.1%	190.6%

DPP-4 = dipeptidyl peptidase-4; NA = not applicable.
*Decrease in expenditure, despite increase in days supply, likely attributable to gliclazide modified release becoming available as a generic in 2008.

7 METHODS

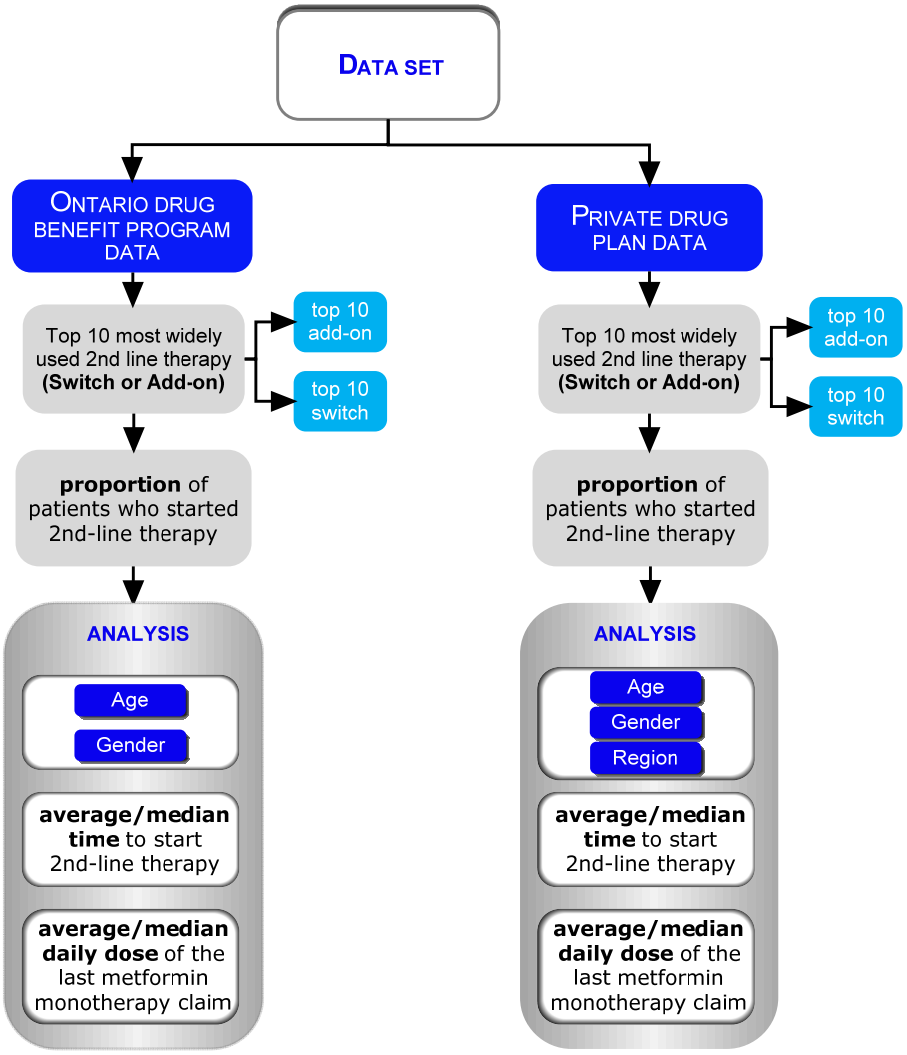
7.1 Data Source

Data used in the analysis were provided by Brogan Inc.'s public and private claims-level database. The public data from the claims-level database were only available for Ontario, and PDP data were reported by region.

7.2 Data Analysis

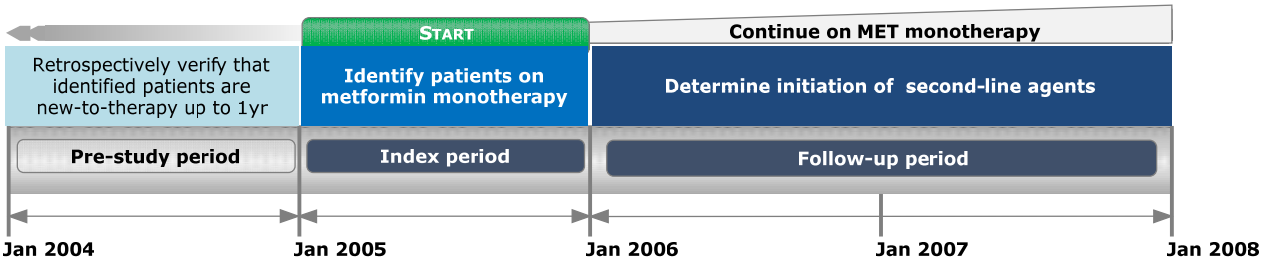
The data were analyzed separately by drug plan (i.e., public versus private). An overview of the analysis, shown in Figure 6, outlines these analyses and subgroup-specific analyses (Figure 6). Detailed methods used for this analysis are presented in the project protocol.

Figure 6: Overview of Analysis



Administrative claims data from publicly and PDPs in Canada formed the basis of this retrospective database analysis. New-to-therapy metformin patients were identified during a one-year period and tracked for up to three years. Their claims were analyzed from an initial claim for metformin monotherapy up to whichever point occurred earlier — an initial claim for a second-line agent or the end of the study period (Figure 7).

Figure 7: Schematic Representation of Current Utilization Analysis of Second-Line Antidiabetes Therapies after Inadequate Control with Metformin Alone



MET = metformin.

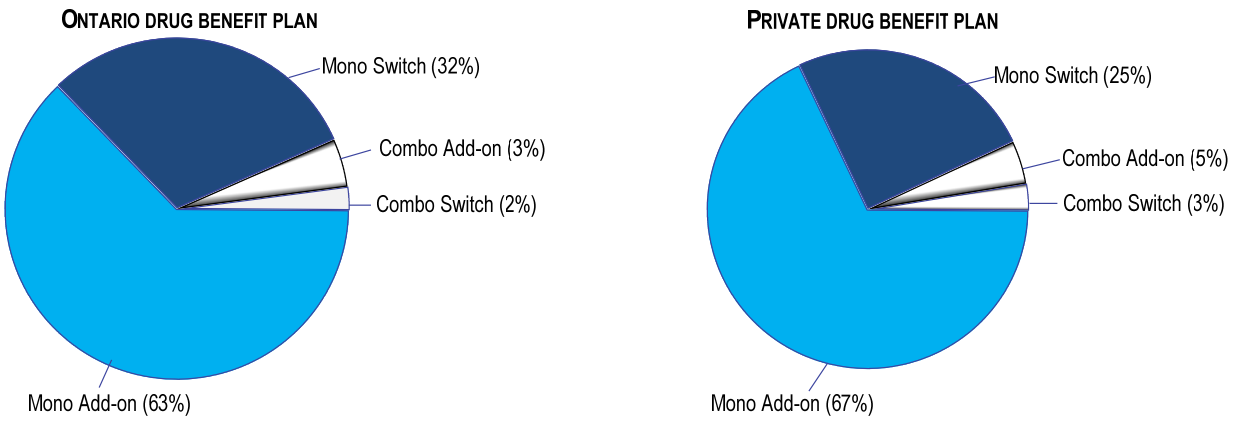
7.3 Cost analysis

Using current drug prices, we estimated the proportion of total costs expended on each second-line agent. Prices for drugs were obtained from the OPDP where available, otherwise prices were obtained from other public drug programs in Canada.[45-49] A 10% markup and $7.00 pharmacy fee per 90-day supply were assumed for all claims. We further assumed that patients used the average defined daily dose (DDD) for each treatment, as defined by the World Health Organization. Insulin doses were based upon a patient sample from British Columbia that was assessed by an endocrinologist member of the COMPUS Expert Review Committee. Annual drug costs calculated in this manner were multiplied by the current utilization data to estimate total proportional costs attributable to each class of second-line antidiabetes drugs.

8 RESULTS

Of the 27,367 patients with type 2 diabetes who had an initial claim for metformin monotherapy in the OPDP in 2005, 9,082 (33%) subsequently claimed at least one second-line antidiabetes drug as of December 31, 2007. Meanwhile in the PDPs, of the 51,771 patients with type 2 diabetes who had an initial claim for metformin monotherapy in 2005, 15,803 (30%) subsequently claimed at least one second-line antidiabetes drug as of December 31, 2007. The majority of patients within both the OPDP and PDPs (63% versus 67% respectively) who claimed a second-line agent received a single drug that was added on to metformin (Figure 8). Many individuals also switched from metformin to monotherapy with a second-line agent (OPDP 32%, PDPs 25%). A much smaller proportion of patients either added on or switched to a combination of second-line agents.

Figure 8: Distribution of Therapeutic Strategies Involving Second-Line Antidiabetes Agents in the OPDP and PDPs



OPDP = Ontario Public Drug Plan.

The average time from the initiation of metformin monotherapy to a claim for a second-line agent was 371.5 ± 185.2 days and 338.5 ± 240.2 days in the public drug plans and PDPs respectively. The average daily dose of metformin monotherapy before failure and a claim for a second-line agent was 1,457.4 mg ± 417.7 mg and 1,495.3 mg ± 268.4 mg for the public and PDPs respectively. The average dose and duration of metformin monotherapy were similar regardless of whether second-line therapy was added to metformin or metformin was discontinued (Table 6).

Table 6: Average Metformin Monotherapy Duration and Dose Before an Initial Claim for a Second-Line Antidiabetes Drug (dependant on whether second-line therapy was added to, or switched from, metformin)

	OPDP			Privately Funded Drug Program		
	Add-On Therapy	Switch Therapy	Overall	Add-On Therapy	Switch Therapy	Overall
Average days to initiation of second-line therapy (± SD)	351.6 ± 171.4	393.0 ± 200.1	371.5 ± 185.2	324.3 ± 236.3	345.3 ± 230.0	338.5 ± 240.2
Average Metformin Daily Dose (mg) (± SD)	1,510.4 ± 361.7	1,400.4 ± 470.8	1,457.4 ± 417.7	1,609.7 ± 273.9	1,388.8 ± 189.2	1,495.3 ± 268.4

OPDP = Ontario Public Drug Program; SD = standard deviation.

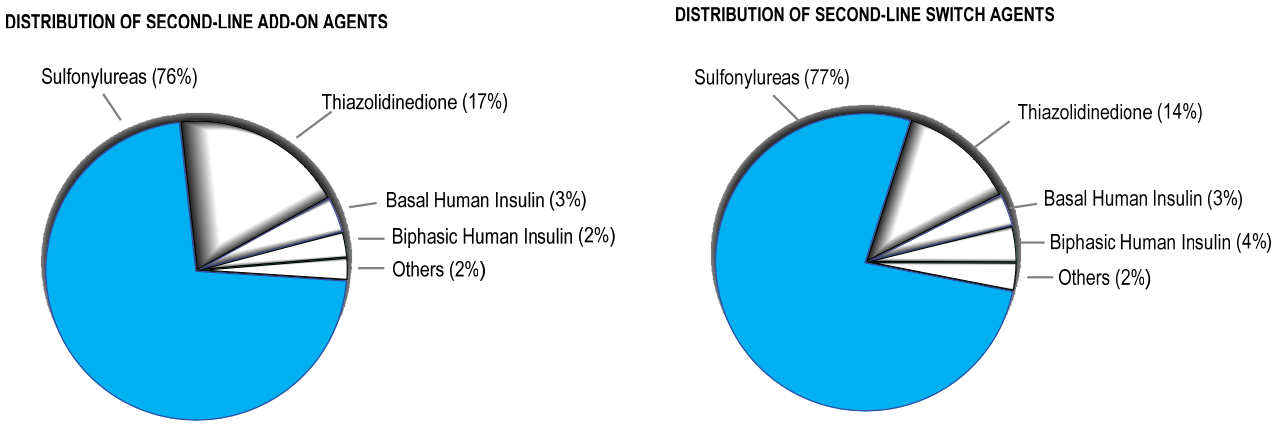
8.1 Ontario Public Drug Program

The top ten second-line agents claimed by OPDP beneficiaries after initial metformin monotherapy are shown in Table 7. More than 76% of beneficiaries submitted a claim for a sulfonylurea. Other agents included rosiglitazone (8.6%) and pioglitazone (7.2%). The distribution of agents used was similar regardless of whether second-line therapy was added to, or switched from, metformin (Figure 9).

Table 7: Top Second-Line Antidiabetes Drug Classes Claimed by Beneficiaries of the OPDP (2006 to 2008) After Initial Metformin Monotherapy			
	Second-Line Drug Class Claimed	**Number of Beneficiaries**	**%**
1	**Sulfonylureas**	**6,663**	**76.4**
2	TZD	1,378	15.8
3	Intermediate-acting Human Insulin	255	2.9
4	Biphasic Human Insulin	216	2.5
5	Alpha-Glucosidase Inhibitors	96	1.1
6	Biphasic Insulin Analogue	46	0.5
7	Meglitinides	42	0.5
8	Rapid-Acting Insulin Analogue	18	0.2

OPDP = Ontario Public Drug Program; TZD = thiazolidinedione.

Figure 9: Distribution of Second-Line Agents Claimed by Beneficiaries of the OPDP (2006 to 2008) after Initial Metformin Monotherapy (dependant on whether second-line therapy was added to, or switched from, metformin)



OPDP = Ontario Public Drug Plan.

Stratification of utilization patterns by age (< 65 versus ≥ 65 years) revealed no significant difference in the distribution of the top 10 second-line agents claimed. Sulfonylureas were still the leading agent (80% versus 75%), followed by the TZDs. Similar trends were observed when utilization was stratified by gender.

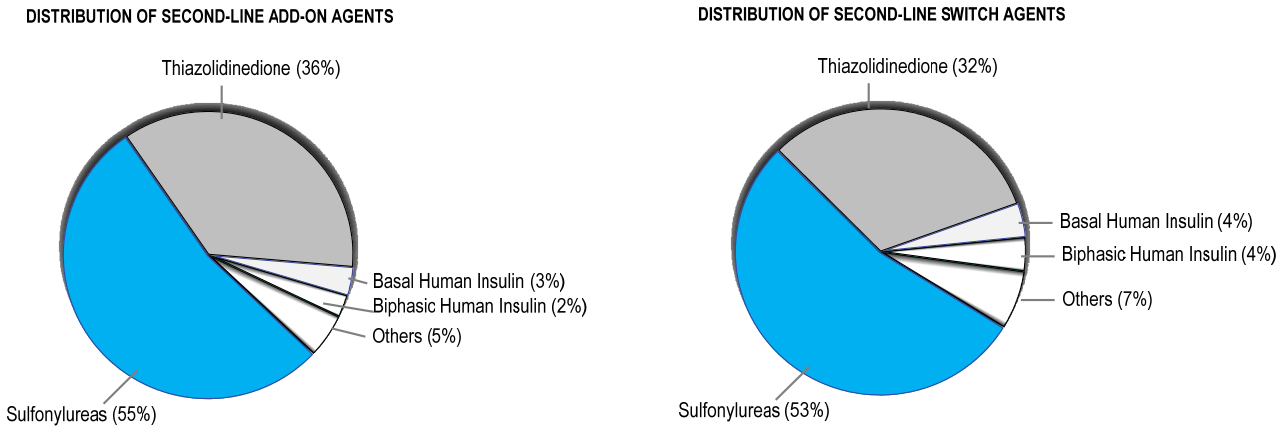
8.2 Private Drug Plans in Canada

In PDPs, more than 55% of beneficiaries that submitted a claim for a second-line agent after initial metformin therapy claimed for a sulfonylurea. Other common drug classes included TZDs and insulin (Table 8). Stratification by an add-on or switch of second-line therapy from metformin indicated that sulfonylureas were claimed by 55% of patients in the former category and 53% in the latter category (Figure 10). The TZDs were claimed as second-line therapy by more than 30% of patients in both categories.

Table 8: Top Ten Second-Line Antidiabetes Drug Classes Claimed by Beneficiaries of PDPs in Canada (2006 to 2008) After Initial Metformin Monotherapy			
	Second-Line Drug Class Claimed	**Number of Beneficiaries**	**%**
1	**Sulfonylureas**	**7,988**	**55.4**
2	TZD	5,030	34.8
3	Meglitinides	674	4.7
4	Intermediate-acting Human Insulin	272	1.9
5	Biphasic Human Insulin	228	1.6
6	Biphasic Insulin Analogue	70	0.5
7	Long-acting Insulin Analogues	69	0.5
8	Alpha-Glucosidase Inhibitors	64	0.4
9	Rapid-Acting Insulin Analogue	36	0.2

PDPs = private drug plans; TZD = thiazolidinedione.

Figure 10: Distribution of Second-Line Agents Claimed by Beneficiaries of PDPs in Canada (2006 to 2008) after Initial Metformin Monotherapy (dependant on whether second-line therapy was added to, or switched from, metformin)

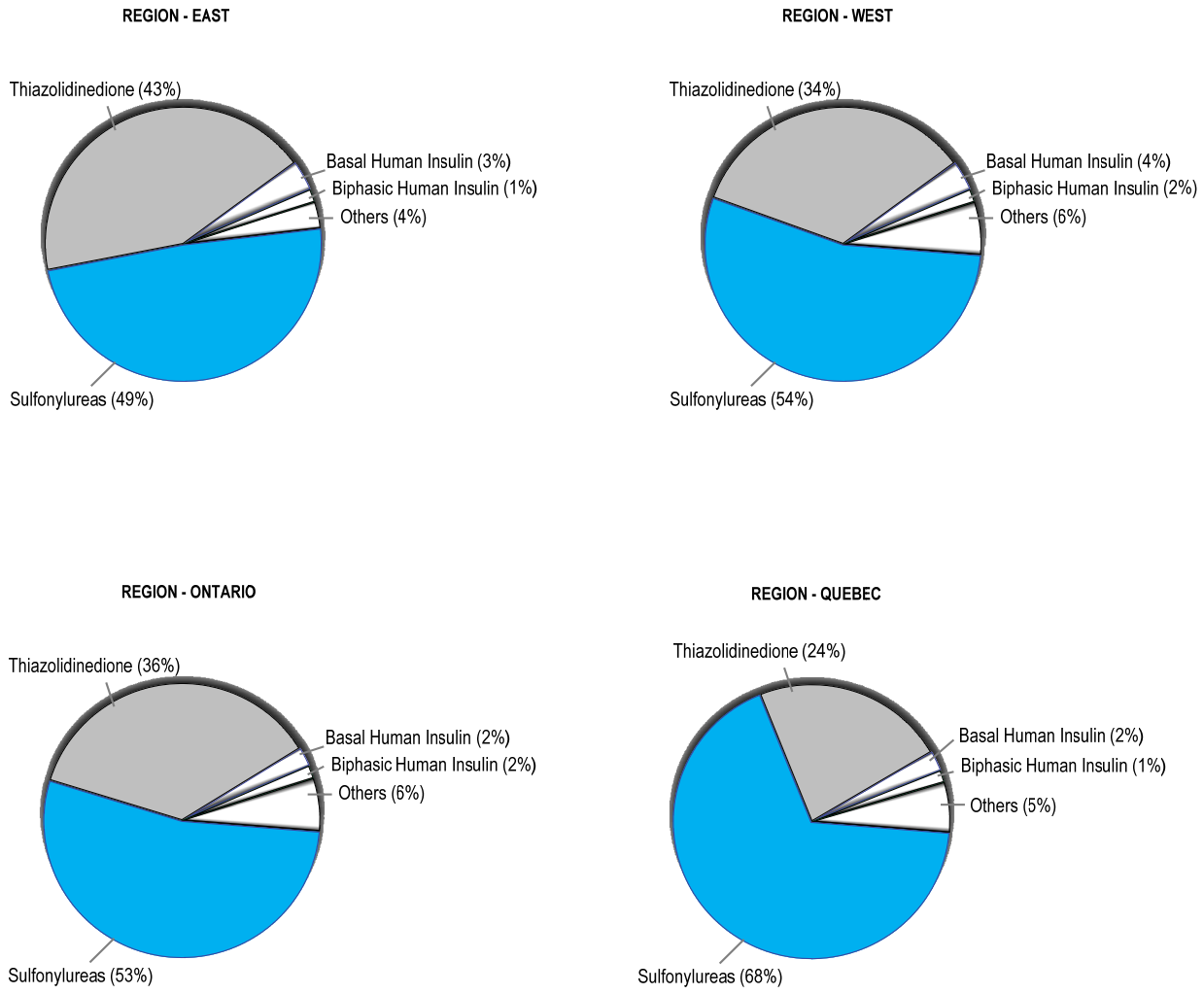


PDP = private drug plan.

Stratification of utilization patterns by age (< 65 versus ≥ 65 years) revealed no significant difference in the distribution of the top second-line agents claimed. Sulfonylureas were still the leading agent (54% versus 65%), followed by the TZDs. Similar trends were observed when utilization was stratified by gender.

Regional utilization data for PDPs showed relatively consistent rankings for second-line agents (Figure 11). The use of sulfonylureas was very similar in Eastern Canada, Western Canada, and Ontario (range 49% to 54%), but substantially higher in Quebec (68%). TZDs were consistently ranked as the next most commonly used second-line agents. Interestingly, the proportion of patients submitting claims for rosiglitazone was nearly twice as high in Eastern Canada than in Quebec (31.1% versus 16.4%). Usage of pioglitazone (range 7.5% to 12.6%) and the meglitinides (range 3.2% to 5.5%) was relatively consistent across regions.

Figure 11: Distribution of Second-Line Agents Claimed by Beneficiaries of PDPs in Canada (2006 to 2008) According to Region



PDPs = private drug plans.

9 METHODS

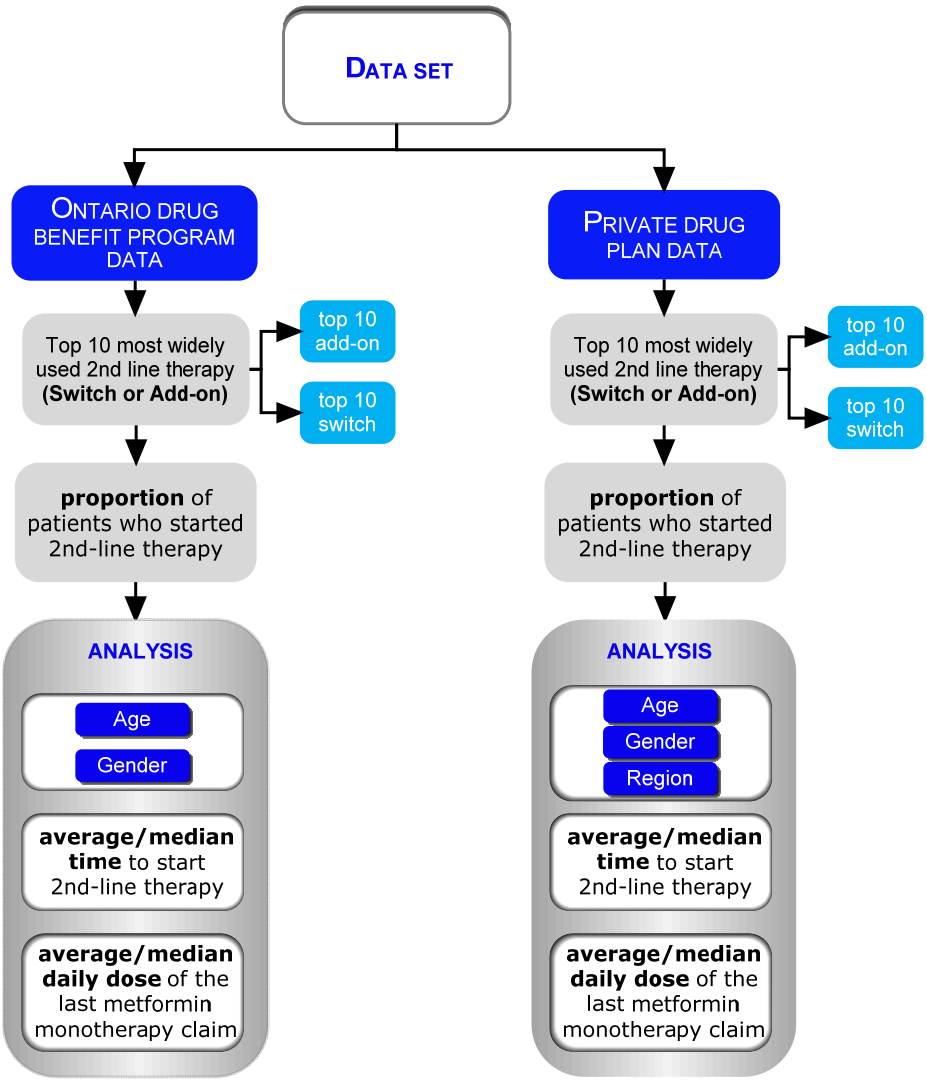
9.1 Data Source

Data used in the analysis were provided by Brogan Inc.'s public and private claims-level database. The public data from the claims-level database were only available for Ontario, and PDP data were reported by region.

9.2 Data Analysis (Third-Line Therapy)

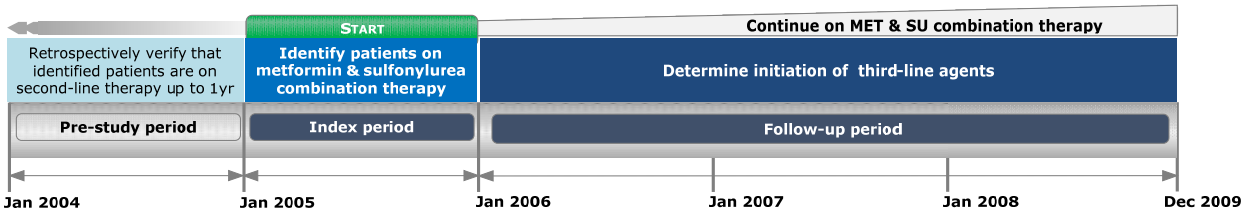
The data were analyzed separately by drug plan (i.e., public versus private). An overview of the analysis, shown in Figure 12, outlines these and subgroup-specific analyses (Figure 12).

Figure 12: Overview of Analysis



Administrative claims data from publicly and PDPs in Canada formed the basis of this retrospective database analysis. Patients on a third-line antidiabetes therapy were identified during a one-year period and tracked for up to four years. For the purposes of the current study, second-line therapy was defined to be concomitant use of metformin and a sulfonylurea. Their claims were analyzed from the initiation of second-line therapy up to whichever point occurred earlier — the point of failure of therapy or the end of the study period (Figure 13).

Figure 13: Schematic Representation of Current Utilization Analysis of Second-Line Antidiabetes Therapies After Inadequate Control with Metformin Alone



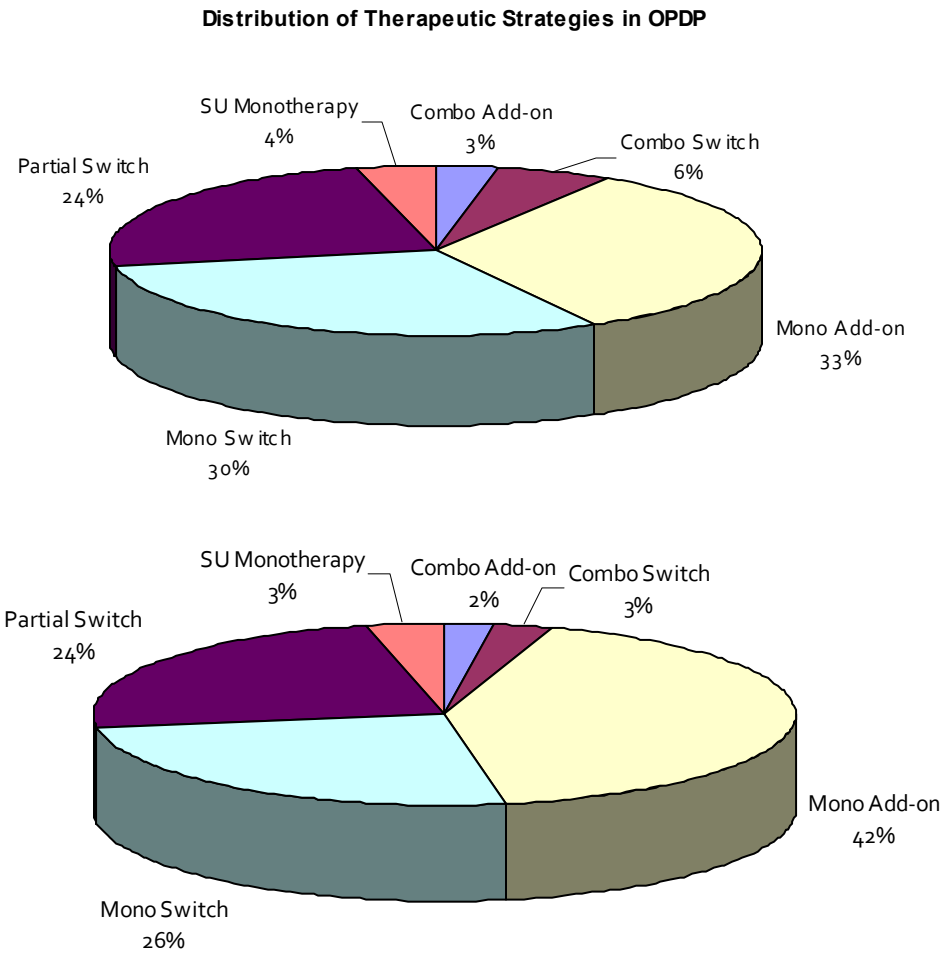
MET = metformin; SU = sulfonylurea.

10 RESULTS

Of the 3,372 patients with type 2 diabetes on a combination therapy of metformin and sulfonylurea in the OPDP in 2005, 1,723 (51%) patients subsequently claimed at least one third-line antidiabetes drug as of December 31, 2009. Meanwhile in the PDPs, of the 5,750 patients with type 2 diabetes on a combination therapy of metformin and sulfonylurea in 2005, 2,677 (47%) subsequently claimed at least one third-line antidiabetes drug as of December 31, 2009. Therefore, these results indicate that in the OPDP and PDPs, 49% and 53% of patients remained on the combination of metformin and a sulfonylurea as second-line therapy to manage their diabetes for at least four years. A greater proportion of patients within both the OPDP and PDPs (33% versus 42% respectively) who claimed a third-line agent received a single drug that was added on to existing metformin and sulfonylurea combination therapy (Figure 14). Many individuals also switched from metformin and sulfonylurea combination therapy to monotherapy with a third-line agent (OPDP 30%, PDPs 26%). Also prevalent, was a partial switch where one of either metformin or a sulfonylurea remained and patients switched to an alternative third-line agent (OPDP 24%, PDPs 24%). A much smaller proportion of patients either added-on or switched to a combination of third-line agents, or remained on sulfonylurea monotherapy.

Figure 14: Distribution of Therapeutic Strategies Involving Third-Line Antidiabetes Agents in the OPDP and Privately Funded Drug Plans (2006 to 2009).

10.1 Ontario Public Drug Program



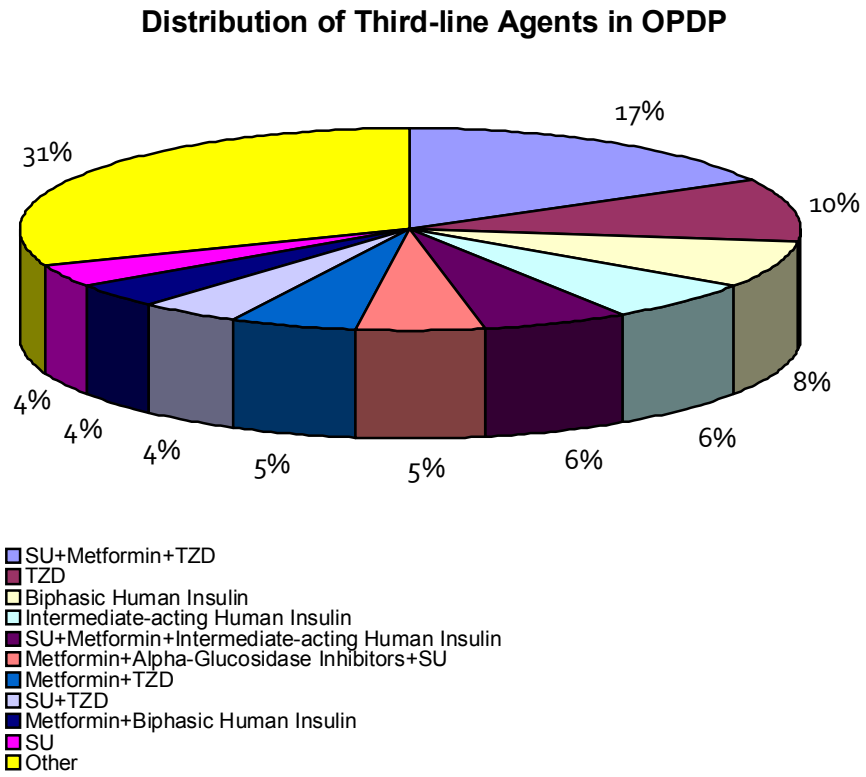
OPDP = Ontario Public Drug Program; SU = sulfonylurea.

The top 10 third-line therapies claimed by OPDP beneficiaries after inadequate control with metformin and sulfonylurea combination therapy are shown in Table 9. Seventeen per cent of beneficiaries submitted a claim for the addition of a TZD to the existing metformin and sulfonylurea combination therapy. Almost 10% of patients dropped metformin and sulfonylurea altogether and switched to TZD exclusively. Both types of human insulin (biphasic and intermediate-acting) were common alone or in various combinations with other agents. Those therapies that are not represented in Table 9 accounted for 31% of the overall distribution and include a variety of combinations and switches. Individually, the therapies represented a very minor proportion (< 1%), but the culmination of these numerous combinations add together to account for a major segment (Figure 15). The relative distribution of agents used was similar across third-line therapies including an add-on, switch, or partial switch (Figure 16).

Table 9: Top Ten Third-Line Antidiabetes Drug Classes Claimed by Beneficiaries of the OPDP (2006 to 2009) after Inadequate Control on Metformin and Sulfonylurea Combination Therapy			
	Second-Line Drug Class Claimed	**Number of Beneficiaries**	**%**
1	**Sulfonylurea plus Metformin plus TZD**	**294**	**17.00**
2	TZD	172	9.95
3	Biphasic Human Insulin	130	7.52
4	Intermediate-acting Human Insulin	109	6.30
5	Sulfonylurea plus Metformin plus Intermediate-acting Human Insulin	105	6.07
6	Metformin plus Alpha-Glucosidase Inhibitors plus Sulfonylurea	95	5.49
7	Metformin plus TZD	90	5.21
8	Sulfonylurea plus TZD	70	4.05
9	Metformin plus Biphasic Human Insulin	67	3.88
10	Sulfonylurea	65	3.76

OPDP = Ontario Public Drug Plan; TZD = thiazolidinedione.

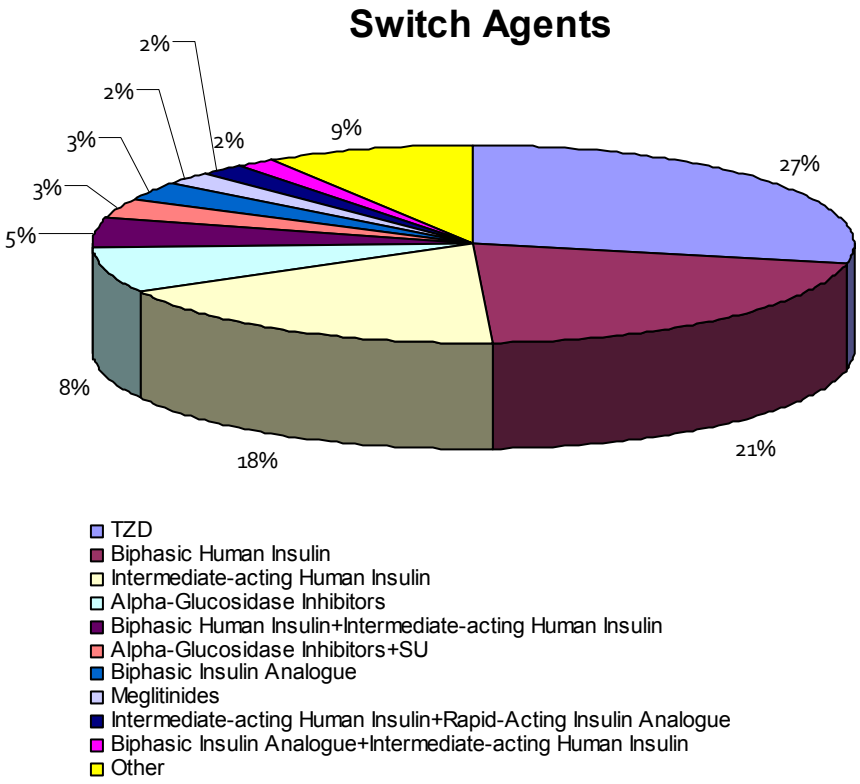
Figure 15: Distribution of Third-Line Agents Claimed by Beneficiaries of the OPDP (2006 to 2009) after Inadequate Control on Metformin and Sulfonylurea Combination Therapy

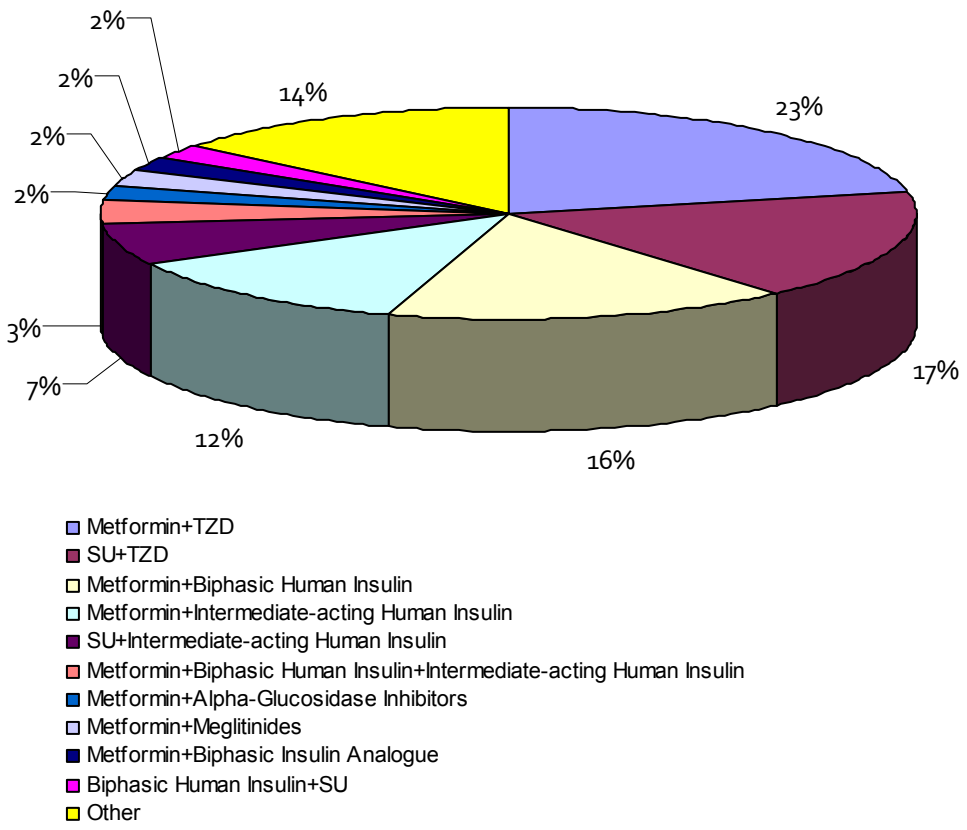


OPDP = Ontario Public Drug Plan; SU = sulfonylurea; TZD = thiazolidinedione.

The higher prevalence of TZD usage as a third-line intervention was similar regardless of whether it was added to, switched, or partially switched from metformin and sulfonylurea combination therapy (Figure 16). The addition of a TZD to existing metformin and sulfonylurea therapy was the most significant (46%), followed by combinations of metformin and sulfonylureas with intermediate-acting human insulin. Usage of TZDs was considerable in this cohort; and when utilization was collapsed across therapies (i.e., any intervention that includes TZD), the analysis showed that 40% of individuals use TZD in some capacity as a third-line strategy.

Figure 16: Distribution of Third-Line Therapies Claimed by Beneficiaries of the OPDP (2006 to 2009) Either Added On or Switched to Metformin and Sulfonylurea Combination Therapy





OPDP = Ontario Public Drug Plan; SU = sulfonylurea; TZD = thiazolidinedione.

10.2 Private Drug Plans in Canada

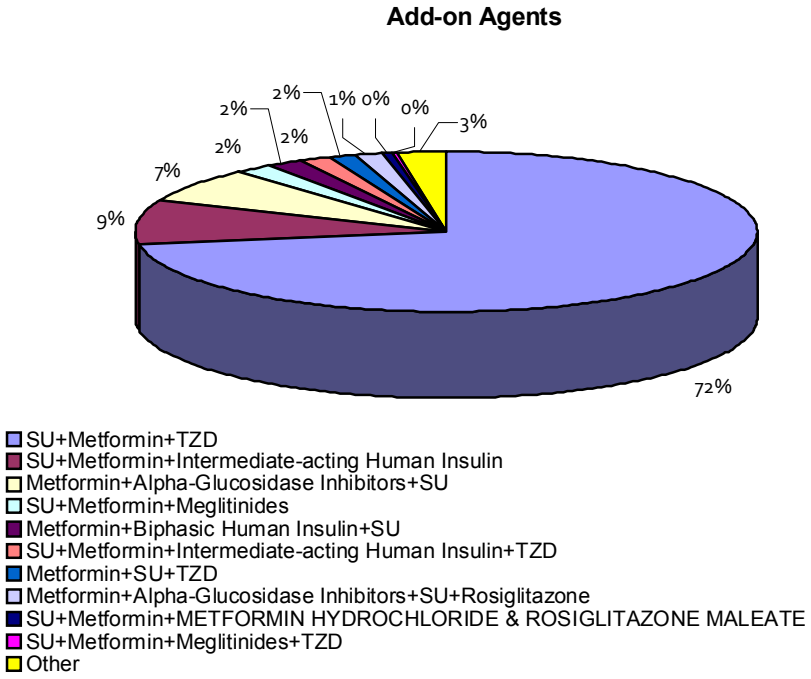
In PDPs, more than 32% of beneficiaries submitting a claim for a third-line agent after inadequate control with metformin and sulfonylurea combination therapy added on a TZD (Table 10). Sixteen per cent submitted a claim switching from existing metformin and sulfonylurea therapy to a TZD. Other common drug classes included TZDs and insulin (Table 10). Both types of human insulin (biphasic and intermediate-acting) were common alone or in various combinations with other agents. Those therapies that are not represented in Table 10 accounted for 20% and include a variety of combinations and switches. Individually, the therapies represented a very minor proportion (< 1%), but the culmination of these numerous combinations add together to account for a major segment (Figure 16).

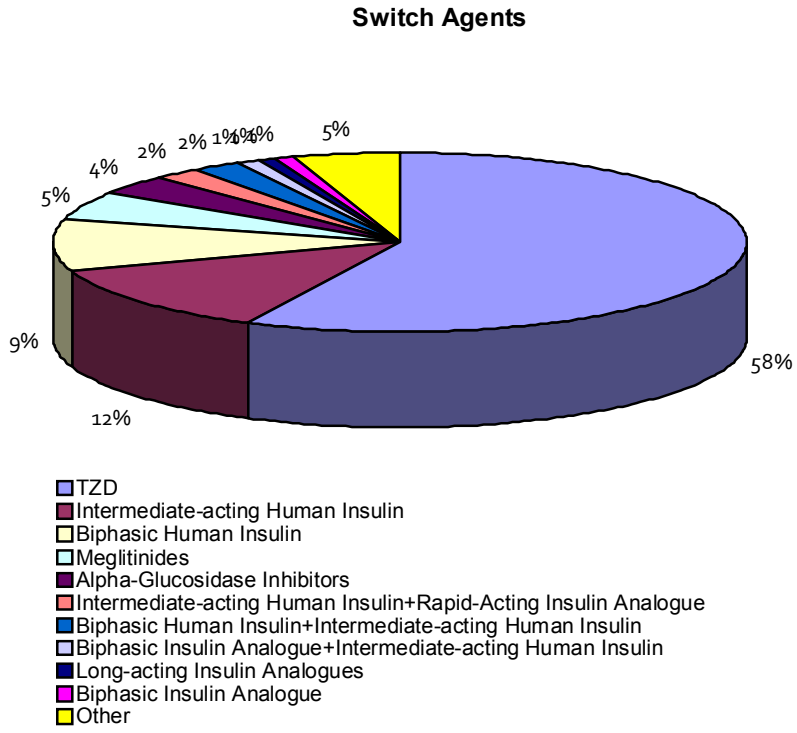
Table 10: Top Ten Third-Line Antidiabetes Drug Classes Claimed by Beneficiaries of PDPs (2006 to 2009) in Canada after Inadequate Control on Metformin and Sulfonylurea Combination Therapy			
	Second-Line Drug Class Claimed	**Number of Beneficiaries**	**%**
1	**Sulfonylurea plus Metformin plus TZD**	**861**	**32.24**
2	TZD	434	16.25
3	Metformin plus TZD	203	7.60
4	Sulfonylurea plus TZD	156	5.84
5	Sulfonylurea plus Metformin plus Intermediate-acting Human Insulin	107	4.01
6	Intermediate-acting Human Insulin	94	3.52
7	Sulfonylurea	89	3.33
8	Metformin plus Alpha-Glucosidase Inhibitors plus Sulfonylurea	82	3.07
9	Biphasic Human Insulin	71	2.66
10	Metformin plus Meglitinides	44	1.65

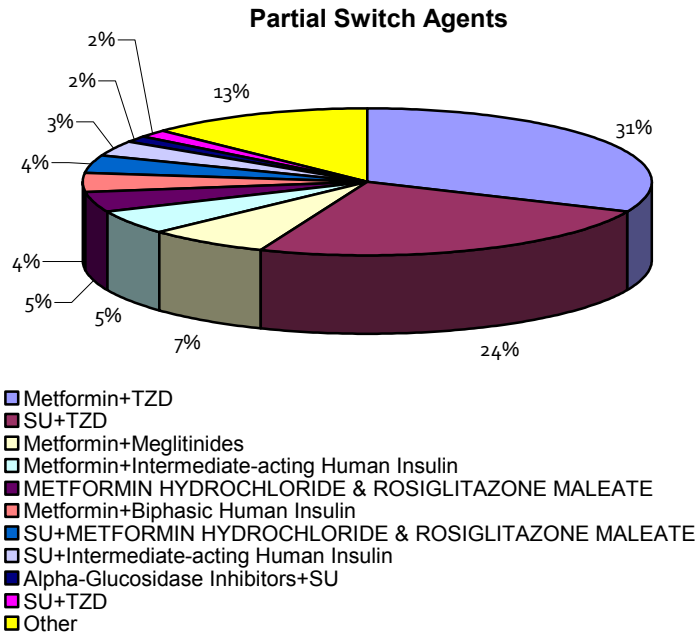
PDPs = private drug plans; TZD = thiazolidinedione.

Utilization of TZDs as a third-line intervention was considerable regardless of whether it was added to, switched, or partially switched from metformin and sulfonylurea combination therapy (Figure 17). The addition of a TZD to existing metformin and sulfonylurea therapy was the most significant (72%), followed by combinations of metformin and sulfonylureas with intermediate-acting human insulin. Fifty-eight per cent of patients switched from metformin and sulfonylurea combination therapy to TZDs. The partial switch away from second-line therapy to TZDs was also significant in patients who dropped either metformin or sulfonylurea (24% and 31% respectively). Overall, usage of TZDs was considerable in this cohort; and when utilization is collapsed across therapies (i.e., any intervention that includes TZD), the analysis shows that 69% of individuals use TZD in some capacity as a third-line strategy.

Figure 17: Distribution of Third-Line Therapies Claimed by Beneficiaries of PDPs (2006 to 2009), Either Added On or Switched to Metformin and Sulfonylurea Combination Therapy



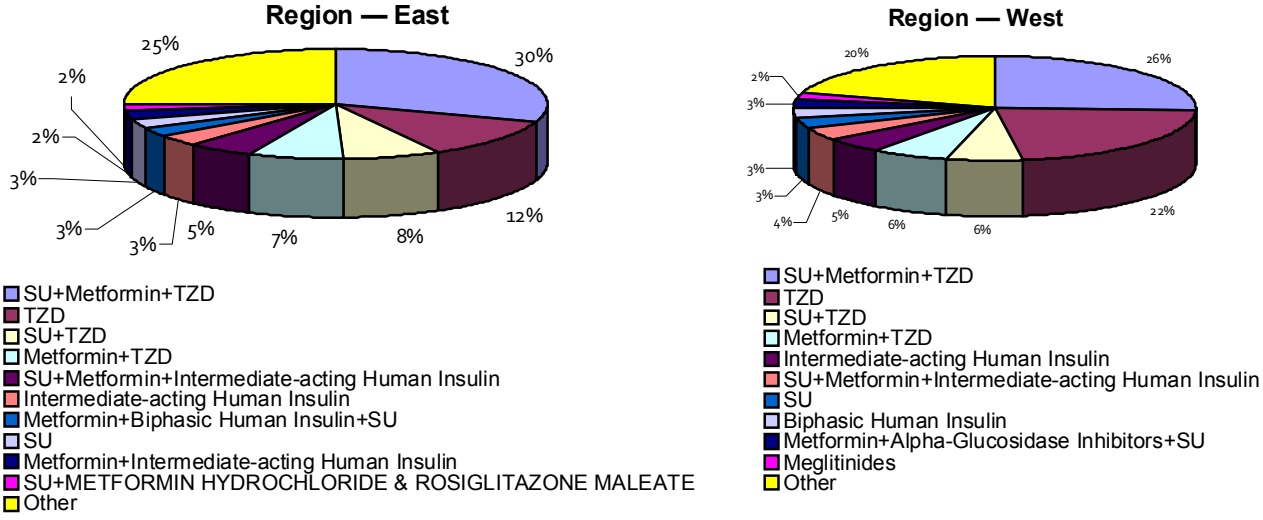


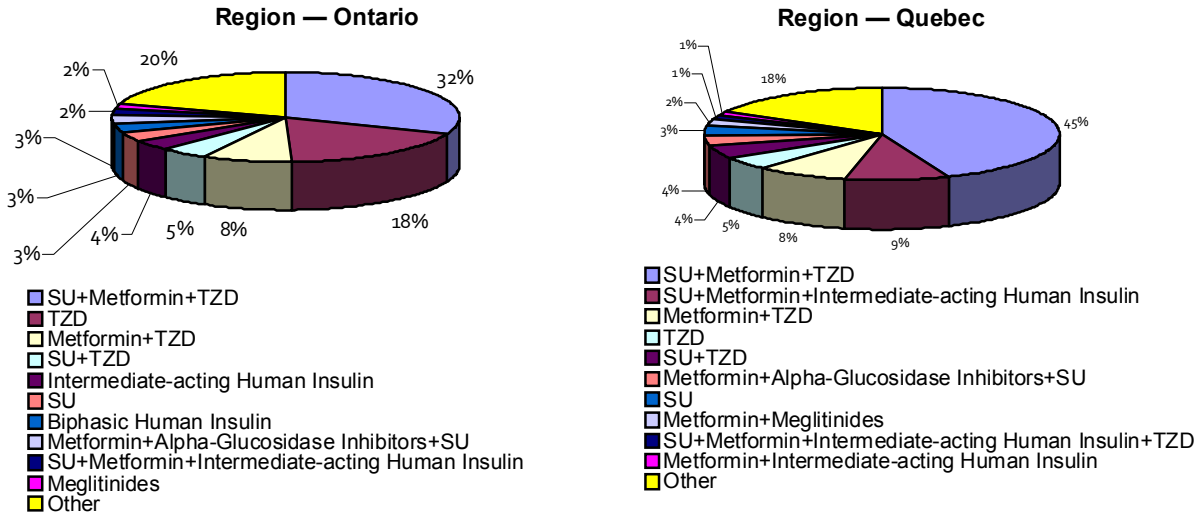


PDPs = private drug plans; SU = sulfonylurea; TZD = thiazolidinedione.

Regional utilization data for PDPs showed relatively consistent rankings for third-line agents (Figure 18). The use of TZDs as an add-on therapy to metformin and sulfonylurea was very similar in Eastern Canada, Western Canada, and Ontario (range 26% to 32%), but substantially higher in Quebec (45%). Switching to TZD monotherapy from second-line therapies was consistently ranked as the second most commonly used third-line agents (except Quebec). Interestingly, the proportion of patients submitting claims for TZD either as an add-on, switch, or partial switch when aggregated from the top 10 interventions was similar and considerable across regions (Eastern Canada — 57%, Western Canada — 60%, Ontario — 63% and Quebec — 62%).

Figure 18: Distribution of Third-Line Agents Claimed by Beneficiaries of PDPs in Canada (2006 to 2009), According to Region





11 DISCUSSION

Lifestyle modification (e.g., diet, exercise) may be sufficient in curbing the progression of type 2 diabetes for many patients. When these become inadequate, most patients initiate metformin monotherapy; however, the ability of metformin to control glycemic levels over the long-term may deteriorate as diabetes progresses over time. In most cases it is necessary for patients to add on another oral antidiabetes agent or agents to achieve or maintain target blood glucose levels. Previous results have shown that the need to control glycemic levels intensifies with the duration of diabetes.[50] This analysis focused on changes in the Canadian oral antihyperglycemic market and utilization patterns of second-line and third-line antidiabetes agents in Canada among patients with type 2 diabetes initially treated with metformin monotherapy.

11.1 Market Share Analysis

During the past 12 years, expenditure on oral antidiabetes drugs in the OPDP and PDPs has increased significantly. Sharp increases in expenditure have been driven primarily by the introduction of newer, more expensive drug classes. A large proportion of total costs (40% to 50%) are expended on newer, more expensive classes of drugs in both public and private drug plans, despite accounting for a small proportion (10% to 15%) of daily use. The annual cost of TZDs or DPP-4 inhibitors greatly exceeds that of older classes of oral drugs. For every one patient treated with a TZD or a DPP-4 inhibitor, you could treat[3] eight or nine patients with a sulfonylurea or metformin. Since 2006 to 2007, we observed a sharp decrease in the utilization of and expenditure on TZDs in both the OPDP and PDPs. This decline in use is likely attributable to safety concerns surrounding the use of rosiglitazone and the introduction of generic pioglitazone.[51-54] The sharp decrease in expenditure since 2007 is likely attributable to both safety concerns and the introduction of generic pioglitazone. In PDPs, we have observed a sharp increase in DPP-4 inhibitors and increased use of metformin and sulfonylureas. In the

[3] Does not include the additional cost of blood glucose test strips; however, patients using sulfonylureas typically use an extra 0.20 test trips per day compared with those using non-hypoglycemia including oral antihyperglycemic drugs. Therefore, this should not have an impact on estimates.

OPDP, we have observed increases in the use of metformin, sulfonylureas, and alpha-glucosidase inhibitors; the OPDP currently does not cover DPP-4 inhibitors.

11.2 Second-Line Therapy

In both publicly and PDPs, the majority of patients who initiated second-line therapy to manage their glycemic levels did so with sulfonylureas (76% and 55% respectively), followed by TZDs. The lower proportion of sulfonylurea usage in PDPs may be attributable to the wider array of drugs that are available as benefits compared with public drug plans. Utilization was dominated by sulfonylureas and TZDs, regardless of whether the therapy was classified as an add-on or switch. Stratification of the data by age or gender did not substantially alter any of the usage patterns. However, analysis by region revealed that sulfonylurea utilization was notably higher in Quebec, while TZD usage was most common in the Atlantic Provinces. Insulins were found to only represent a small proportion of second-line agent utilization (between 3% and 5%) within both public and PDPs. It is not surprising that insulin is not commonly used as a second-line agent, given the inconvenience associated with injecting insulin, the need for more stringent self-monitoring, and the higher cost compared with other agents.

The high prevalence of sulfonylurea use as second-line therapy in the current analysis is not unexpected as this aligns with an unpublished analysis of private and provincial drug plans showing that this class was second only to metformin in terms of the number of claims for oral antidiabetes agents.[6] Pharmacy claims data for oral antidiabetes agents across Canada for the year ending May 2008 further support this finding, with the number of sulfonylurea prescriptions second only to metformin.[17]

In the current analysis, the average duration of time to the addition of, or switch to, a second-line agent in both the public and private drug plans was approximately one year. It is important to note that this only represented the 33% of beneficiaries within both the OPDP and PDPs that claimed a second-line agent within the observed time frame. Consequently, we were unable to estimate the median time from the initiation of metformin monotherapy to the requirement for a second-line agent. Previous studies have reported that by three years after diabetes diagnosis, approximately 50% of patients require the addition of a second-line therapy, and by nine years this number approaches 75% of patients.[8]

Thirty-two per cent of OPDP beneficiaries and 25% of private plan beneficiaries were found to have switched from metformin to a second-line agent, rather than continue to take metformin. Metformin is recommended as the first-line oral antidiabetes drug in most patients with type 2 diabetes when glycemic control cannot be achieved by lifestyle interventions alone, with second-line agents added to metformin as required to achieve glycemic control.[1-5] Indeed, a Current Practice analysis[55] conducted by CADTH in this area revealed that most health professionals believed metformin should be continued along with secondary agents unless there were intolerable adverse effects or contraindications.[15,56] Metformin is associated with gastrointestinal adverse events (range 2% to 63%),[57] particularly during the initiation of therapy.[58] This may be the cause for the relatively high rates of switching observed in this analysis. Other reasons for switching may have been the development of contradictions to metformin, such as renal failure or the perceived lack of efficacy. The reasons underlying the discontinuation of metformin in favour of other antidiabetes agents deserve further investigation so that strategies aimed at improving prescribing and utilization of antidiabetes therapies can be targeted appropriately.

11.3 Third-Line Therapy

Roughly half of the patients from the second-line cohort were inadequately controlled with metformin and sulfonylurea combination therapy and required third-line therapy. In both the public and private plans, most patients opted to add on a single agent to their existing metformin and sulfonylurea combination therapy, in most cases this was a TZD. Another significant portion of this inadequately controlled population switched away from their combination therapy to TZD monotherapy. In addition, a considerable portion of patients partially switched away from the combination therapy and kept either metformin or sulfonylurea and added on a TZD. Utilization of TZDs when collapsed across groups shows that in public plans, 40% of beneficiaries use a TZD in some capacity as a third-line agent, as do 69% of beneficiaries in the PDPs. Interestingly, combination therapy involving metformin, a sulfonylurea and a TZD (rosiglitazone), or TZD with any insulin agent (synthetic or human), to manage glycemic control is not indicated in Canada.[58] This demonstrates that TZD utilization as a third-line intervention is prevalent even though this is in opposition to its suggested role.

A key strength of this analysis is that it was longitudinal in nature, allowing for precise identification of patients new to metformin monotherapy, subsequent analysis of second-line agents prescribed, and quantification of the dose and duration of metformin before second-line therapy was initiated. However, there were also some limitations. First, claims level data for publicly funded drug plans were available for the OPDP only. Thus, utilization of second-line therapies in other publicly funded drug programs in Canada could not be estimated. Second, it is possible that utilization patterns from 2005 and 2007 are not entirely reflective of current practice because of the availability of newer agents, publication of recent evidence, changes in formulary listings, or other factors. Furthermore, as with other cross-sectional data, the time frame of the analysis may not have been sufficient to capture changes to treatment regimens. Indeed, only about one-third of patients initiated on metformin monotherapy subsequently claimed a second-line agent. A longer duration of follow-up would have allowed for a more accurate estimation of median time to failure of metformin monotherapy; however, we can presume that average time to failure would be much greater than one year. Concerns surrounding the safety of TZDs became evident[51-54] during the study period of the cohort used in this third-line portion of the current utilization analysis, and as a consequence the results may not be reflective of the actual usage of TZDs for third-line therapy at present. Finally, our analysis only provides information on second- and third-line agents claimed by beneficiaries; the degree to which treatments claimed were actually consumed is unknown.

12 CONCLUSION

During the past 12 years, utilization and expenditure on oral antidiabetes drugs in the OPDP and PDPs has increased significantly. A large proportion of total expenditure in both public and PDPs has been spent on newer more expensive agents despite lower utilization of them. Newer drug classes are much more expensive than older drug classes — for each patient treated with either a TZD or a DPP-4 inhibitor you could treat eight to nine patients with a sulfonylurea or metformin. Based on an analysis of the OPDP and PDPs in Canada, the majority of patients use sulfonylureas after their diabetes is inadequately controlled on metformin alone. Most patients add a sulfonylurea to existing metformin monotherapy, a pattern that is consistent across age, gender, and region. However, a significant proportion of patients abandoned metformin monotherapy. In the PDPs, utilization patterns are comparable

across geographical regions, although sulfonylurea usage was highest in Quebec, and the proportion of patients using a TZD was highest in Eastern Canada. Most patients in both public and private plans who require a third-line agent, add on a TZD to their existing combination therapy of metformin and a sulfonylurea. TZD usage is considerable despite not being indicated for this application in Canada. Many patients also abandon combination therapy with metformin and a sulfonylurea and switch to a TZD. Indeed, the results of this analysis, in combination with the available evidence regarding the relative clinical and cost-effectiveness of the various classes of antidiabetes agents, can help policy-makers and clinicians develop and implement strategies to optimize the treatment of type 2 diabetes in Canada.

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